Claims

1. A method for identifying a mutation in a nucleic acid molecule encoding a polypeptide that inhibits RNA interference (RNAi), said method comprising:

(a) providing a mutagenized nematode comprising a gene that is expressed in a cell that is refractory to RNAi;

(b) contacting said nematode with an inhibitory nucleobase oligomer that targets said gene; and

(c) detecting a decrease in the expression of said gene in said mutagenized nematode relative to a control nematode, wherein a mutation in a nucleic acid molecule encoding a polypeptide that inhibits RNAi is identified by said decrease in the expression of said targeted gene.

2. The method of claim 1, wherein said decrease is detected by monitoring the expression of a reporter gene.

3. The method of claim 1, wherein said cell is a neuron.

4. The method of claim 1, wherein said inhibitory nucleobase oligomer is a dsRNA, siRNA, or dsRNA mimetic.

5. The method of claim 1, wherein said mutation identifies said nucleic acid molecule.

6. A method for identifying a mutation in a nucleic acid molecule encoding a polypeptide that inhibits RNAi, said method comprising:

(a) providing a mutagenized cell expressing a gene that is refractory to RNAi;

(b) contacting said cell with an inhibitory nucleobase oligomer that targets said refractory gene; and

(c) detecting a decrease in the expression of said gene, wherein a mutation in a nucleic acid molecule encoding a polypeptide that inhibits RNAi is identified by detecting said decrease.

7. The method of claim 6, wherein said cell is a nematode cell.

8. The method of claim 6, wherein said cell is a mammalian cell.

9. The method of claim 6, wherein said decrease is detected by monitoring the expression of a reporter gene.

10. The method of claim 6, wherein said mutation identifies said nucleic acid molecule.

11. A method for identifying a candidate compound that enhances RNAi, said method comprising:

(a) providing a cell expressing an *eri-1* nucleic acid molecule;

(b) contacting said cell with a candidate compound; and

(c) comparing the expression of said *eri-1* nucleic acid molecule in said cell contacted with said candidate compound with the expression of said *eri-1* nucleic acid molecule in a control cell, wherein a decrease in said expression identifies said candidate compound as a candidate compound that enhances RNAi.

12. The method of claim 11, wherein said screening method identifies a compound that decreases transcription of said nucleic acid molecule.

13. The method of claim 11, wherein said screening method identifies a compound that decreases translation of an mRNA transcribed from said nucleic acid molecule.

14. The method of claim 11, wherein the compound is a member of a chemical library.

15. The method of claim 11, wherein said cell is in a nematode.

16. A method for identifying a candidate compound that enhances RNAi, said method comprising:

(a) providing a cell expressing an ERI-1 polypeptide;

(b) contacting said cell with a candidate compound; and

(c) comparing the biological activity of said ERI-1 polypeptide in said cell contacted with said candidate compound to a control cell, wherein a decrease in said biological activity of said ERI-1 polypeptide identifies said candidate compound as a candidate compound that enhances RNAi.

17. The method of claim 16, wherein said cell is a nematode cell.

18. The method of claim 17, wherein said cell is in a nematode.

19. The method of claim 16, wherein said cell is a mammalian cell.

20. The method of claim16, wherein said cell is a plant cell.

21. The method of claim 16, wherein said ERI-1 polypeptide is an endogenous polypeptide.

22. The method of claim 16, wherein said biological activity is monitored with an enzymatic assay.

23. The method of claim 16, wherein said biological activity is monitored with an immunological assay.

24. The method of claim 16, wherein said biological activity is monitored by detecting degradation of an ERI-1 nucleic acid substrate.

25. The method of claim 23, wherein said nucleic acid substrate is an siRNA.

26. A method for identifying a candidate compound that enhances RNAi, said method comprising:

(a) providing an ERI-1 polypeptide;

(b) contacting said polypeptide with a candidate compound; and

(c) detecting binding of said ERI-1 polypeptide and said candidate compound, wherein a compound that binds to said ERI-1 polypeptide is a candidate compound that enhances RNAi.

27. The method of claim 23, wherein said candidate compound binds to and blocks an ERI-1 active site.

28. A method for identifying a candidate compound that enhances RNAi, said method comprising:

(a) providing an ERI-1 polypeptide and a nucleic acid substrate;

(b) contacting said ERI-1 polypeptide and said nucleic acid substrate with a candidate compound under conditions suitable for substrate degradation; and

(c) detecting a decrease in substrate degradation in the presence of said candidate compound relative to substrate degradation in the absence of said candidate compound, wherein a decrease in said substrate degradation identifies said candidate compound as a candidate compound that enhances RNAi.

29. The method of claim 28, wherein said nucleic acid substrate is an siRNA.

30. The method of claim 28, wherein said nucleic acid substrate is coupled to a fluorophore.

31. A method for identifying a candidate compound that enhances RNAi, said method comprising:

(a) providing a cell expressing an ERI-1 polypeptide;

(b) contacting said cell with a dsRNA in the presence of a candidate compound; and

(c) monitoring a dsRNA-related phenotype in said cell in the presence of said candidate compound relative to said phenotype in the absence of said candidate compound, wherein an alteration in said phenotype identifies said candidate compound as a candidate compound that enhances RNAi.

32. An isolated ERI-1 polypeptide comprising an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO:2, wherein said polypeptide inhibits RNAi.

33. An isolated nucleic acid molecule comprising a nucleotide sequence having at least 90% identity to the nucleotide sequence encoding SEQ ID NO:2, wherein expression of said nucleic acid molecule in an organism inhibits RNAi in said organism.

34. A vector comprising the isolated nucleic acid molecule of claim 26.

35. A host cell comprising the vector of claim 34.

36. An antibody that specifically binds to an ERI-1 polypeptide.

37. An organism comprising a mutation in an *eri-1* nucleic acid sequence, wherein said mutation enhances RNAi in said organism.

38. The organism of claim 37, wherein said organism is a nematode.

39. The organism of claim 37, wherein said organism is a mammal.

40. The organism of claim 30, wherein said organism is a plant.

41. An isolated nucleobase oligomer comprising a duplex comprising at least eight but no more than thirty consecutive nucleobases of an *eri-1* nucleic acid, wherein said duplex when contacted with an *eri-1* expressing cell, reduces *eri-1* transcription or translation.

42. The oligomer of claim 41, wherein said duplex comprises a first domain comprising between 21 and 29 nucleobases and a second domain that hybridizes to said first domain under physiological conditions, wherein said first and second domains are connected by a single stranded loop.

43. The oligomer of claim 41, wherein said loop comprises between 6 and 12 nucleobases.

44. The oligomer of claim 41, wherein said loop comprises 8 nucleobases.

45. The oligomer of claim 41, wherein said oligomer reduces the level of expressed ERI-1 polypeptide.

46. A nucleobase oligomer comprising a first region, wherein said first region comprises at least eight but no more than thirty consecutive nucleobases corresponding to an *eri-1* nucleic acid molecule, and a second region, wherein said second region comprises at least eight but no more than thirty consecutive nucleobases complementary to said first region, and said oligomer when contacted with an *eri-1*-expressing cell, reduces *eri-1* transcription or translation.

47. The nucleobase oligomer of claim 46, wherein said nucleobase oligomer is an shRNA.

48. The nucleobase oligomer of claim 46, wherein said nucleobase oligomer comprises at least one nucleic acid modification.

49. The nucleobase oligomer of claim 46, wherein said modification is a modified sugar, nucleobase, or internucleoside linkage.

50. The nucleobase oligomer of claim 46, wherein said modification is a modified internucleoside linkage selected from the group consisting of phosphorothioate, methylphosphonate, phosphotriester, phosphorodithioate, and phosphoselenate linkages.

51. The nucleobase oligomer of claim 46, wherein said nucleobase oligomer comprises at least one modified sugar moiety.

52. The nucleobase oligomer of claim 46, wherein said nucleobase oligomer comprises RNA residues.

53. The nucleobase oligomer of claim 52, wherein said RNA residues are linked together by phosphorothioate linkages.

54. An expression vector encoding a nucleobase oligomer comprising a duplex comprising at least eight but no more than thirty consecutive nucleobases of an *eri-1* nucleic acid, wherein said duplex, when contacted with an *eri-1*-expressing cell, reduces *eri-1* transcription or translation.

55. An expression vector encoding a nucleobase oligomer comprising a first region, wherein said first region comprises at least eight but no more than thirty consecutive nucleobases corresponding to an *eri-1* nucleic acid molecule, and a second region, wherein said second region comprises at least eight but no more than thirty consecutive nucleobases complementary to said first region, and said oligomer when contacted with an *eri-1*-expressing cell, reduces *eri-1* transcription or translation.

56. The expression vector of claim 54 or 55, wherein a nucleic acid sequence encoding said nucleobase oligomer is operably linked to a promoter.

57. The expression vector of claim 56, wherein said promoter is the U6 PolIII promoter, polymerase III H1 promoter.

58. A cell comprising the expression vector of claim 54 or 55.

59. The cell of claim 58, wherein said cell is a transformed human cell that stably expresses said expression vector.

60. The cell of claim 58, wherein said cell is *in vivo*.

61. The cell of claim 58, wherein said cell is a human cell.

62. The cell of claim 58, wherein said cell is a neoplastic cell.

63. A transgenic organism expressing a nucleic acid sequence encoding an *eri-1* nucleobase oligomer, wherein said nucleobase oligomer inhibits the expression of an endogenous *eri-1* nucleic acid sequence.

64. The organism of claim 63, wherein said organism is a mammal.

65. The organism of claim 63, wherein said organism is a nematode.

66. The organism of claim 63, wherein said organism is a plant.

67. A method for enhancing RNAi in an organism, said method comprising contacting said organism with a nucleobase oligomer of claim 46 in an amount sufficient to enhance RNAi.

68. The method of claim 67, wherein said organism is a plant.

69. The method of claim 67, wherein said organism is a mammal.

70. The method of claim 67, wherein said organism is a pathogen, selected from the group consisting of a bacteria, a virus, a fungus, an insect, or a nematode.

71. The method of claim 67, wherein said nucleobase oligomer is an siRNA or an shRNA.

72. A pharmaceutical composition comprising an *eri*-1 nucleobase oligomer and an excipient.

73. A double-stranded RNA corresponding to at least a portion of an *eri-1* nucleic acid molecule of an organism, wherein said double-stranded RNA is capable of decreasing the level of ERI-1 polypeptide encoded by an *eri-1* nucleic acid molecule.

74. An antisense nucleic acid molecule, wherein said antisense nucleic acid molecule is complementary to at least six nucleotides of an *eri-1* nucleic acid molecule, and wherein said antisense nucleic acid molecule is capable of decreasing expression of an ERI-1 polypeptide from an *eri-1* nucleic acid molecule.

75. A method for identifying an siRNA having enhanced RNAi activity, said method comprising:

(a) contacting a test siRNA with an ERI-1 polypeptide under conditions suitable for RNA degradation;

(b) measuring the amount of undegraded test siRNA relative to a control siRNA known to be degraded under similar conditions, wherein increased resistance to degradation indicates that said test siRNA has enhanced RNAi activity.

76. An siRNA capable of inducing enhanced RNAi, said siRNA comprising a 3' terminus having at least 2 cytosine or guonosine **bases**, such that said siRNA resists degradation by ERI-1.

77. An isolated *eri-1* inhibitory nucleic acid comprising at least a portion of a naturally occurring *eri-1* nucleic acid molecule of an organism, or its complement, where the *eri-1* nucleic acid encodes a polypeptide selected from the group consisting of any or all of the following T07A9.5, BC035279, T04799, BC035279, BAB02568.1, NP_566502.1, T04799, NP_921413.1, NP_179108.1, AAL31944.1, AAL84996.1, CAB36522.1, CAB79531.1, AAK98687.1, AAP53700.1, NP_499887.1, NP_500418.1, NP_741292.1, NP_741293.1, T28707, NP_508415.1, NP_497750.1, NP_507742.1, T15066, AAB94148.1, T29900, AAB09126.1, AAK39277.2, NP_741293.1, T32575, AAK39278.1, T28707, NP_508415.1, Q10905, YWO2_CAEEL, T30086, AAA82440.1, AAP57300.1, NP_741293.1, NP_507945.1, T19258, NP_505050.1, T32575, AAK39278.1, T26693, CAA20983.1, T33294, AAC17749.1, AK064632.1, AP002897.2, AK103348.1, AK062026.1, AY105868.1, NM_112377.1, AF419612.1, AF419612, AY079112.1, AP002862.2, AP000815.1, AP003103.2, AK120298.1, NM_191971, AY112398.1, AC146855.5, AY105981.1, NM_117213.2, AF291711.1, AF291711, AK120333.1, AK106560.1, AB019236.1, AK122166.1, NM_184142.1, NM_196431.1, and AC093544.8, or an ortholog of any or all of these *eri-1* nucleic acid molecules, where the *eri-1* inhibitory nucleic acid comprises at least a portion of a naturally occurring *eri-1* nucleic acid molecule, or is capable of hybridizing to a naturally occurring *eri-1* nucleic acid molecule, and decreases expression from a naturally occurring *eri-1* nucleic acid molecule in the organism.